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TITLE: Redefining Gulf War Illness Using Longitudinal Health Data: The Fort Devens Cohort

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13. SUPPLEMENTARY NOTES

14. ABSTRACT-Shortly after return from Gulf War (GW) deployment in 1991, some GW veterans began reporting a constellation of health symptoms that did not meet criteria for well-defined medical conditions or syndromes. Symptoms included pain, cognitive deficits, skin rash, gastrointestinal difficulties and sleep problems. The initial attempts at identifying case definition used a one-time cross-sectional health symptom report, which is insufficient for determining a case definition given that symptoms often show remitting and relapsing tendencies. Current estimates suggest that 25 percent of GW veterans (nearly 170,000) have reported persisting multisymptom illness and in order to stimulate more appropriate treatment avenues for ill veterans, it is essential that a refined case definition be found taking change over time into account and examining the impact of symptoms previously reported on current health status. This will be accomplished by employing a longitudinal design with a large longitudinally followed cohort. Current health symptom survey data will therefore be compared with prior survey data. The practical application of this study is to provide a gold standard definition to be used in future treatment trials. The study goals include, devising a new case definition for GW illness, where possible assisting in the management of specific disease states, and collecting outcome data about treatment avenues employed and their efficacy. Year 1 goals have primarily been met including designed a web based health symptom to correspond with prior pen and pencil formats and obtaining necessary IRB and human use approvals to begin survey recruitment efforts.

15. SUBJECT TERMS- Persian Gulf War, Neurotoxicants, Neuropsychology, Health Symptoms, PON1, Symptom Trajectory, Case Definition

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Introduction

Background and Purpose: Current estimates suggest that 25 percent of Gulf War (GW) veterans (nearly 170,000) have reported some type of persisting multi-symptom illness. Currently used GW Illness (GWI) case definitions have been found to be lacking in sensitivity and specificity with many veterans falling in the false positive and false negative ranges. These GWI definitions, based on cross-sectional studies, allow for reporting of health symptoms only once, and do not consider that symptoms can emerge over time (or remit); thus they likely provide inaccurate representations of veterans' health. Only through the use of longitudinal data, where health symptoms were first measured shortly after deployment and then repeatedly over the following 20 years, would consideration of symptom trajectories and patterns of change over time be possible in order to refine the case definition of GWI. The Ft. Devens, MA cohort was designed as a longitudinal cohort and included nearly 3,000 soldiers. This cohort will be useful in ameliorating the existing problems with case definition. The ultimate goal for this study is to provide a consistent case definition of GWI, which can serve future studies and treatment trials as a valid outcome.

Scope: The true value of a longitudinal prospective design such as the Ft. Devens cohort is that it can capture symptom trajectories that may have been modified by treatment effects. Data mining from the multiple time points during the last 19-years in the Ft. Devens cohort now allows for a more refined case definition of GW illness that can take change over time into account and examine the impact of symptoms previously reported on health, genetic vulnerabilities and treatment outcomes. The practical application of this enhanced case definition of GWI is to provide a gold standard definition for the case ascertainment and evaluation of future treatment trials. Although originally designed as a prospective longitudinal study to compare changes over time, this has not been reported in the Ft. Devens cohort to date. Therefore, the current

investigators have a unique opportunity to capitalize on the strengths of this cohort and perform a Time 4 follow up health symptom inquiry to evaluate the utility of prior case criteria and using longitudinal data improve upon case definition classification. The Ft. Devens data, maintained at the Behavioral Science Division for PTSD at the VA Boston Healthcare System, is fully accessible to the current study PI through the password protected shared drive. The existing database will be combined with the current survey findings in order to compare and contrast symptoms in order to determine the new case definition. Reliability of responses will be determined with the use of validity checks as was done with prior datasets.

A question naturally arises how longitudinal characterization could result in a gold-standard case definition for GW illness. This will be accomplished by developing algorithms of risk factors for developing chronic health symptoms that would be encountered by ill GW veterans. The risk factors that would be included in the algorithm equation would include health symptom report, genetic vulnerabilities (PON1 status) and prior treatment effectiveness. This model closely resembles the Framingham Heart Study risk model equations that have used longitudinal health symptom and biomarker patterns to develop risk algorithms for development of chronic disease states including stroke and cardiovascular disease (i.e. heart attacks etc.). This risk algorithm for GW illness could then be translationally employed by VA primary care physicians as well as GW illness researchers.

Body

The approved statement of work for the first year study period is below:

STATEMENT OF WORK

Redefining Gulf War Illness Using Longitudinal Health Data: The Fort Devens Cohort

Months 1-6:

Task 1: Finalize Plan for Participant Recruitment

1a. Submit human use documents for IRB approvals.

1b. Receive health symptom comparison data from Ft. Devens Cohort Studies Time 1, 2, and 3.

1c. Identify current address and contact information for surviving members of the Time I cohort of 2,949 participants

Months 4-9:

Task 2: Finalize Methods for Web Survey Design

2a. Format completed health symptom questionnaires for use with teleform and website

2b. Create website for collection of current health symptom status, health care utilization and treatment usage with collaboration from DCC

Months 9-36:

Task 3: Data Collection and Deliverables

3a. Send pre-survey letter to original cohort participants with an "opt-out" postcard for those not wishing to participate

3b. Obtain demographic information and information pertaining to current health status and changes in medical or psychiatric diagnoses by use of web-based survey and by mail questionnaire for those individuals who do not have access to a computer

3c. Follow-up calls made to individuals who have not responded. Complete health questionnaires on the phone for individuals not otherwise able to participate

3d. Contact a subsample of 200 survey responders to participate in the genetic testing

3e. Data cleaning and preliminary analyses will be ongoing as data is collected in order to formulate an advanced algorithm case definition for GW Illness

Summary progress to date for year 1 statement of work:

- For this 4th resurvey of the Ft. Devens cohort, initial study start-up work for this first year has included submitting and obtaining IRB approval for VA Boston Healthcare System, Boston University School of Medicine and CDMRP Human Research Protections Office (HRPO). Work is near completion on the web pages for the planned web survey and study personnel have been meeting biweekly with programmers to ensure successful completion. In addition, Dr. Krengel has obtained access to the prior survey data from the Ft. Devens cohort to compare with the current resurvey study. In addition, cohort contact information collected in 2004 was obtained and study PI has been rechecking records. A research associate has been hired and has completed IRB training. The "with out compensation" VA status was recently obtained for study personnel so that they may access contact information for the original Ft. Devens cohort members. Initial subject recruitment of web survey data will begin shortly and will continue throughout the rest of the study period. Data analyses will be ongoing as data is collected.

Statement of Work Year 1:

Months 1-6: Finalize Plan for Participant Recruitment

Task 1 a. Submit human use documents for IRB approvals.

- IRB approval has been obtained from the VA Boston Healthcare System Institutional Review Board, Boston University School of Medicine, and HRPO.

Task 1 b. Receive health symptom comparison data from Ft. Devens Cohort Studies Time 1, 2, and 3.

- The PI has obtained access to the database stored behind the VA firewall at the VA Boston Healthcare System.

Task 1 c. Identify current address and contact information for surviving members of the Time I cohort of 2,949 participants.

- Addresses from study participants have been gathered from the last set of Ft. Devens surveys collected in 2004. Study personnel have begun checking contact information.

Months 4-9: Finalize Methods for Web Survey Design

Task 2 a. Format completed health symptom questionnaires for use with Teleform and website

- Questionnaires have been formatted for web conversion and paper questionnaires were programmed into web format to ensure a consistent and complete dataset for this fourth health symptom survey of the Ft. Devens cohort.

Task 2 b. Create website for collection of current health symptom status, health care utilization and treatment usage using web based programming.

- The PI and BU Site PI have met regularly with the BU data coordinating center staff (DCC) to discuss ways to implement the online survey and initial programming is completed. Study personnel have recently been piloting the web survey for implementation with study participants.

Months 9-36: Data Collection and Deliverables

Task 3 a. Send pre-survey letter to original cohort participants with an "opt-out" postcard for those not wishing to participate.

- Presurvey letters will be sent shortly when the web survey questionnaire has been fully tested and is ready for implementation.

Task 3 b. Obtain demographic information and information pertaining to current health status and changes in medical or psychiatric diagnoses by use of web-based survey and by mail questionnaire for those individuals who do not have access to a computer.

- The web survey will be implemented in the first quarter of year 2 after all contact information has been obtained from study participants and the opt-out postcards have been returned.

Task 3 c. Follow-up calls made to individuals who have not responded. Complete health questionnaires on the phone for individuals not otherwise able to participate.

- Follow-up calls with study participants who have not responded will occur in the second quarter of year 2 and proceed until recruitment is complete.

Task 4 d. Data cleaning and preliminary analyses will be ongoing as data is collected in order to formulate an advanced algorithm case definition for GW Illness, an assessment of current health care utilization and treatment efficacy.

- Preliminary data analysis will begin in quarter 3 of year 2 and proceed throughout the rest of the study funding period as web survey data is collected.

Key Research Accomplishments:

- IRB approvals were obtained and initial human use was approved for this study protocol.
- Written questionnaires that have been used for prior Ft. Devens survey studies have been converted into web format for initiation of the web survey. Special care has been taken to ensure ease of self-administration for the internet based survey.
- Potential study participants have been identified from the Ft Devens cohort, those previously surveyed upon arriving home from deployment to the Gulf War.
- Randomized code numbers were generated for each potential survey participant to have a de-identified code number when completing the web survey.
- Longitudinal health symptom data has been collected from prior surveys and entered into a database that will allow for combination with subsequently collected data (Time 4).
- Study participant reimbursement codes for Amazon.com have been obtained to compensate participants for study participation.

Reportable Outcomes:

Presentations

Krengel, M., Janulewicz, P., Chamberlian, J., Yuan, J., Valmas, M & Sullivan, K**.** Gulf War Illness: A meta-analytic review of cognitive findings. International Neuropsychological Society, 40th Annual Meeting, Montreal, Canada, February 2012.

Sullivan, K & Krengel, M. Chronic Health Effects of Pesticide Exposure in Military Pesticide Applicators. Paper presented at the doctoral seminar Boston University School of Public Health on November 23, 2011.

Sullivan, K**.** Structural MRI and Cognitive Correlates in Pest-control Personnel from Gulf War I. Paper presented at the Research Advisory Committee on Gulf War Veterans Illnesses: Summer meeting, Boston, MA, June 2012.

Sullivan, K. Neurotoxicity of Gulf War Deployment: The Neuropsychological and Neuroimaging Correlates. Paper presented at the continuing education seminar at the Palo Alto VA on July 12, 12.

Publications

Sullivan, K., Killiany, R., Powell, F., Krengel, M., Pinto, L., Proctor, S.P., Heeren, T., White, R.F. Objective Biomarkers of Gulf War Illness: Structural MRI and Diffusion Tensor Imaging. Neurotoxicology and Teratology, submitted with requested revisions.

Sullivan, K., Krengel, M., Janulewicz, T., and Chamberlain, J. An overview of toxicant exposures in Veteran cohorts from Vietnam to Iraq. In Amara, J. ,Hendricks, A.(eds) (2013) *Military medical care: From predeployment to post- separation,* Abingdon: Routledge.

Manuscripts in Preparation (from previous DoD funding sources)

- Sullivan, Krengel et al., Neuropsychological Functioning in Military Pesticide Applicators from Gulf War I: Effects on Information Processing speed and Visual Memory.

- Krengel, Sullivan et al., Chronic Health Symptoms in Military Pesticide Applicators from Gulf War I.

- Janulewicz-Lloyd, Sullivan, Krengel et al., Gulf War Illness: A meta-analytic review of cognitive findings.

- Sullivan, Krengel, Janulewicz-Lloyd et al., Gulf War Illness: A meta-analytic review of health symptom report findings.

Grant funding

Dr. Krengel and Dr. Sullivan have recently applied for three Gulf War-related grants as either PI or as collaborators with other GW investigators. All three proposals were recommended for grant funding and are listed below.

Title: GW110054 - "Intranasal Insulin: A Novel Treatment for Gulf War Multisymptom Illness" (PI: Golier, Co-PIs Krengel; Sullivan)
Supporting agency: Department of Defense (W81XWH-12-1-0585)
Specific aims: (1) To assess the efficacy of two different doses (10 IU BID and 20 IU BID) of daily intranasal insulin for eight weeks on memory and attention functioning in GW veterans with CMI. (2) To assess the efficacy of two different doses of intranasal insulin on overall physical health and mood in GW veterans with CMI. (3) To characterize the effect of different doses of intranasal insulin on other symptoms that are characteristic of or associated with CMI (e.g., fatigue, pain, sleep quality, subjective cognitive function). (4) To assess the safety of two different doses of self-administered intranasal insulin in GW veterans with CMI.

Title: Identification of Plasma Biomarkers of Gulf War Illness Using "omic" Technology" (PI:Crawford; Co-I Krengel)
Supporting Agency: CSR&D (CX000469-01A1)
Specific aims: The aim of this project is to develop a plasma biomarker panel by using targeted "omic" investigations and screening an additional GW Veteran population to qualify the biomarker findings from the discovery phase by determining the reproducibility of the diagnostic specificity and sensitivity of the candidate biomarkers under investigation. This novel and innovative proposal addresses many of the outstanding needs pertaining to issues related to GWI, a) diagnostic biomarkers, b) differences in biological responses due to genetic heterogeneity, c) personalized medicine. Biomarkers may also be identified which can be used as surrogates for evaluation of therapeutic efficacy.

Title: Brain Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness Consortium (GWIC) (PI: Sullivan, Co-I Krengel)
Supporting agency: Department of Defense (CDMRP/GWIRP GW120037)
Specific aims: This multisite consortium will undertake a coordinated series of clinical and preclinical studies aimed at providing a comprehensive understanding of the pathobiology of GWI. This will include clinical studies conducted in parallel at three sites (Boston, Miami,

and Central Texas) that will collect data on veterans with GWI and healthy controls that includes brain imaging, neuropsychological testing, and diverse immune and genetic measures. Parallel preclinical studies will evaluate persistent effects of GW neurotoxicants *in vitro* and in rodent models of GWI. Findings from clinical and preclinical studies will be compared and used to identify specific brain-immune pathways that can be targeted for treatment intervention.

Conclusions to date:

This study has the unique potential of using longitudinal health symptom reports to compare trajectories of health symptoms over time in ill Gulf War veterans over a 20-year time span. This will not only provide the ability to further understand health symptom trajectories over time but will also allow for the determination of a newly revised case definition of GW illness. Accomplishments to date have included modernizing health survey techniques for ease of administration with secure web-based technologies. This will also reduce the time burden on participants as skip codes for non-relevant follow-up questions are now included. The web survey programming is now complete and is being tested by research personnel before going live with study participants. We do not anticipate problems with recruitment of participants from this prospectively followed longitudinal cohort of Gulf War veterans.